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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,874	CORNISH, VIRGINIA W.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,55 and 56* is/are pending in the application.

4a) Of the above claim(s) *1-29,55 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see paragraph 11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a amendment, which was dated on February 13, 2006.

Status of the Claims

2. Claims 1-54 were pending. Applicant canceled claims 41-54 and added claims 55 and 56. Therefore, claims 1-40, 55 and 56 are currently pending (e.g., see 2/24/05 amendment).

3. Applicant's response to the Restriction and/or Election of Species requirements is acknowledged (Applicant elected ***without traverse*** Group V, claims 30-40, 55 and 56) and claims 1-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

4. Please note: Applicant's elected species (Subgroup 4 = DHFR-LexA; Subgroup 6 = yeast; Subgroup 7 = lacZ reporter; Subgroup 8 = competitive binding) was found in the art. Furthermore, Applicant's *specifically* elected species (Subgroup 2 = cephen moiety disclosed on page 49 of specification; Subgroup 3 = penicillin-binding-protein; Subgroup 5 = R61-B42 fusion) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the

search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 55 and 56 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see 5/6/05 Response, page 3, "For Subgroup 5 ... [c]laims 30-40 are readable on the elected species").

6. Therefore, claims 30-40 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group V (claims 30-40, 55 and 56) **with traverse** is acknowledged.

8. The traversal is on the following grounds:

[1] "The inventions of claims 1, 5, 15-22, 30-40 and 55-56 are not independent ... The methods of claims 30-40 and 55-56 use the compounds described in claims 1 and 5 to screen a pool of candidate molecules for binding to exogenous fusion protein expressed in the cells of claims 15-22. The methods of claims 30-40 and 55-56 can be pacticed with the compound structure described in claims 1 and 5 and the cells described in claims 15-22 to determine which molecules bind to a known target receptor. Applicant therefore maintains that the claims 1, 5,

15-22, 30-40 and 55-56 are not independent and restriction is not proper" (e.g., see 2/24/05 Response, page 16, last paragraph).

[2] "Furthermore, under MPEP § 809.03, restriction of claims which are 'linked' by one or more 'linking' claims inseparable therefrom is improper. A claim to practicing a process 'links' apparatus and process claims, see MPEP § 809.03©. Claims 30-40 and 55-56 are drawn to processes employing the compounds and cells described in claims 1, 5, and 15-222. Thus, claims 1, 5, and 15-22 are 'linked to claims 30-40, and 55-56." (e.g., see 2/24/05 Response, page 17, paragraph 1).

[3] "... there would not be a serious burden on the Examiner if restriction is not required ... because a search for the prior art material to the patentability of the claims of any of elected claims 30-40 and 55-56 would necessarily turn up the prior art material to the patentability of the claims of Groups 1, 5 and 15-22" (e.g., see 2/24/05 Response, page 17, last paragraph).

This is not found persuasive for the following reasons:

[1] First, the Examiner notes that the method of Group V (i.e., claims 30-40, 55 and 56) do not require the compounds in Group I or the cells in Group V and, as a result, the Groups are not necessarily related. For example, Group V does not require the H1-Y-H2 structure (e.g., see 35 U.S.C. 112, second paragraph rejection below, denoted B). In addition, a product and a method of use can be properly restricted even if they are not "independent" of each other in accordance with MPEP § 806.05(h) i.e., they must be independent or distinct (e.g., see 6/16/04 Restriction Requirement, page 4, paragraph 6).

[2] Again, the Examiner notes that the method of Group V is not necessarily linked to the other Groups. For example, Group V does not require the H1-Y-H2 structures shown in claim 1

of Group 1 (e.g., see 35 U.S.C. 112, second paragraph rejection below, denoted B). In addition, Applicant's interpretation of linking claim practice is not consistent with MPEP 806.05(h). That is, if Applicant's assertions were true then MPEP §806.05(h) would be rendered meaningless as all methods of use are necessarily "linked" to the products that they use. Consequently, this is an unreasonable interpretation of the rule. Furthermore, product claims are not "inseparable" from method claims. In fact, they are recognized as different statutory classes of inventions (e.g., see 35 U.S.C. 101). Finally, the Examiner notes that where an application includes claims to distinct inventions as well as linking claims, restriction can nevertheless be required. See 809 and 821.04(a).

[3] The Examiner respectfully disagrees. For example, as noted above, Group V does not require the H1-Y-H2 structures shown in claim 1 and, as a result, the searches are not co-extensive (e.g., see 35 U.S.C. 112, second paragraph rejection below, denoted B). Furthermore, the mere presence of any alleged overlapping subject matter would not constitute a coextensive search because each Group would have to be searched to its full extent and not just to the extent of any overlapping subject matter, which would, as a practical matter, encompass non-overlapping subject matter and hence result in a non-coextensive search. Consequently, a search burden has been established for the reasons of record.

9. Applicant's election of species is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/or 37 CFR 1.111(b)).

10. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

11. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 4/24/06, 5/23/05, 5/6/05, 11/5/04, 10/10/03, 8/20/02, 5/7/02).

Specification

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 U.S.C. 112, second paragraph

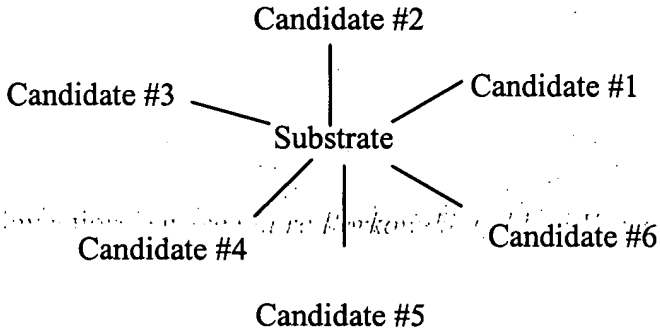
The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 30-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 30** recites the limitation "the small molecule" in step (e). There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 30 and all dependent claims are rejected under 35 USC 112, second paragraph.

B. For **claim 30**, Applicant must claim subject matter which he regards as his own invention (e.g., see *In re Borkowski and Van Venrooy* 164 USPQ 642, 645 (CCPA 1970) ("§112 actually requires claims 'particularly pointing out and distinctly claiming the subject matter which applicant regards as his invention' (emphasis added) … this means that applicant must particularly point out and distinctly claim the subject matter sought to be patented). However, Applicant's current claims require "forming a screening molecule by covalently bonding each molecule in the pool of candidate molecules to a substrate", which would produce molecules of the type:



However, Applicant's specification makes clear that the current application is drawn to molecules of the type H_1-Y-H_2 and their methods of use in chemical dimerization (e.g., see abstract; see also drawing, especially figure 19 showing example of chemical dimerizaqtion using a molecule of the form H_1-Y-H_2). Thus, Applicant has failed to claim his own invention. Therefore, claim 30 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. For ***claim 30***, the phrase, "capable of selectively binding to and selectively forming a covalent bond with a receptor" is vague and indefinite because it is unclear whether the candidate molecule, substrate or entire molecule (i.e., candidate-substrate) is

capable of selectively binding to and selectively forming a covalent bond with a receptor. Therefore, claim 30 and all dependent claims are rejected under 35 USC 112, second paragraph.

D. For ***claims 30 and 37***, the term "small" is a relative term that renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification fails to provide a definition for the term and a person of skill in the art would not recognize the metes and bounds of such a term. Therefore, claims 30, 37 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. **Claim 33** recites the limitation "the transcription activation domain" in line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 33 and all dependent claims are rejected under 35 USC 112, second paragraph.

F. **Claim 36** recites the limitation "the molecule" in line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 36 and all dependent claims are rejected under 35 USC 112, second paragraph.

G. **Claim 38** recites the limitation "the candidate molecule" in step (b). There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 38 and all dependent claims are rejected under 35 USC 112, second paragraph.

H. For **claim 38**, the term "providing a screening molecule having a ligand which has a specificity for the unknown target receptor" is vague and indefinite. For example, it is not clear how a person can provide a ligand that is specific for a receptor without

knowing at least something about the receptor to which the ligand binds? Likewise, it is not clear how a person would know that the substrate is capable of forming a covalent bond with the receptor when the receptor is unknown? That is, the specificity could not be determined without this information. Thus it is not clear in what sense the target is unknown? Applicant is requested to clarify and/or correct. Therefore, claim 38 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 30-40 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicant's claims are directed to a broad genus of methods for identifying molecules that bind to a known target. The method employs at least two-fusion proteins, a DNA with a reporter gene and a screening molecule (e.g., a yeast three-hybrid assay). Independent claim 30, however, places no structural limitations on any of these

molecules. That is, the claims define these terms functionally (e.g., see independent claim 30 substrate is described as having the ability to form a covalent bond to an unidentified receptor). Furthermore, the dependent claims also fail to limit one or more of these constituents with structural limitations (e.g., see dependent claim 35 wherein part of one fusion proteins is limited to PCP R61, but the other fusion protein and the screening molecule still reads on virtually an infinite number of possibilities). Thus, Applicant is claiming the use of the entire universe of possible fusion protein "dimerization" systems without exception. In addition, Applicant also claims the use of the entire universe of "trimerization", "tetramerization", etc., systems (e.g., see 35 U.S.C. 112, second paragraph below).

In contrast, Applicant's specification sets forth only one working example of the claimed method (e.g., see specification, Example 4). In this example, the non-covalent "GR-Dex" portion of the yeast three-hybrid-system shown in figure 13 was replaced with the "R61 PBP-cephem" group to provide a "covalent" interaction. That is, LexA-GR was replaced with LexA-R61 and Dex-Mtx was replaced with cephem-Mtx. The cepehm-Mtx was apparently synthesized by "analogy" to the Dex-cephem-Mtx shown in figure 21 (e.g., see specification, page 50, paragraph 1). In addition, one other "potential" species was suggested as being useful in this regard (e.g., see specification, page 49 where Fluorouracil-thymidylate synthase was disclosed; see also claim 34 wherein the thymidine synthase was claimed), but there is no evidence that a chemical inducer of dimerization ("CID") using this species (i.e., fluorouracil) was ever synthesized and tested.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). Furthermore, a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). Here, Applicant has failed to provide a definition, structure, formula or chemical name for any of the compounds (e.g., screening molecule, first fusion protein, second fusion protein, etc.) used in the claimed method. In addition, the CAFC has stated that a genus, which is set forth only in functional terms, "... is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (1997)). Here, Applicant's claimed screening method employs molecules and fusion proteins that can only be distinguished from other compounds by their function. For example, claim 30, step (a) defines the "substrate" in purely functional terms (i.e., the ability of the substrate to selectively bind and to selectively form a covalent bond with an unidentified receptor), which was held to be impermissible in *Lilly*. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate insulin DNA in *Lilly*,

neither does the generic term "substrate" or "substrate capable of selectively binding to and selectively forming a covalent bond with a receptor" provide an adequate written description for this broad class of screening molecules because the term "substrate" only defines what the compound does (i.e., it ability to react or interact with an unidentified receptor) rather than what it is (i.e., a molecular formula). Likewise, the first and second fusion proteins are reporter genes are only set fort in functional terms (e.g., see claim 30, step (b) wherein Applicant described only one domain of the fusion protein in functional terms and the other domain is not described at all). In fact, this case is even more egregious than *Lilly* because there is no "genetic code" to correlate the structure with the function.

In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the nature of the claimed compounds would depend on a vast number of undefined screening molecules, fusion proteins and reporter genes that do not share any common attributes.

Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the enormous genus. In addition, there is no known generally accepted method for producing the wide array of compounds used in the claimed methods. Thus, the claims fail to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result (i.e., dimerizing two

fusion proteins for the purposes of screening), far beyond those means actually discovered or contemplated by the inventor (i.e. using cephem-Mtx to dimerize LexA-R61 to DHFR-B42), so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

15. Claims 30-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cephem-Mtx induced dimerization of LexA-R61 to DHFR-B42, does not reasonably provide enablement for the use of any screening molecule with any set of fusion proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention

based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicant's claims are directed to a broad genus of methods for identifying molecules that bind to a known target. The method employs at least two-fusion proteins, a DNA with a reporter gene and a screening molecule (e.g., a yeast three-hybrid assay). Independent claim 30, however, places no structural limitations on any of these molecules. That is, the claims define these terms functionally (e.g., see independent claim 30 substrate is described as having the ability to form a covalent bond to an unidentified receptor). Furthermore, the dependent claims also fail to limit one or more of these constituents with structural limitations (e.g., see dependent claim 35 wherein part of one fusion proteins is limited to PCP R61, but the other fusion protein and the screening molecule still reads on virtually an infinite number of possibilities). Thus, Applicant is claiming the use of the entire universe of possible fusion protein "dimerization" systems without exception. In addition, Applicant also claims the use of the entire universe of "trimerization", "tetramerization", etc., systems (e.g., see 35 U.S.C. 112, second paragraph below). Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The art is unpredictable and in its infancy. For example, Abida et al. state, "[w]hile several three-hybrid systems have been reporter, little has been done to characterize these systems and understand the influence of the CID and protein-chimera structure on the transcription

read-out [i.e., the art is in its infancy]" (e.g., see Abida, et al, page 887, column 1, paragraph 1; see also page 893, last paragraph, "Despite this potential generality, little has been done to characterize the influence of the small-molecule-protein interaction on the transcription read-out"). In addition, Abida et al. show that the art is unpredictable. For example, Abida et al. state, "The inherent assumption is that the small molecules and protein chimeras can be varied without disrupting the transcription read-out. Yet, there are anecdotal reports of high-affinity ligand-receptor pairs that cannot be detected with this assay ... The most intriguing result is that, though it is well established that both eDHFR and mDHFR bind Mtx with affinity in the low pm range, only the eDHFR-Mtx interaction activates transcription significantly in this system. This result provides a clear-cut example of related high0-affinity small-molecule-protein interactions that give different levels of transcription activation in the yeast three-hybrid system [i.e., this is a "classic" example of unpredictability]; see also page 893, last paragraph, "Surprisingly, we find that, though both proteins are inhibited by Mtx with picomolar affinity, the transcription read-out for the two differs dramatically" (e.g., see Abida et al., pages 892 and 893). That is, a person of skill in the art would have predicted both eDHFR and mDHFR to activate transcription because, according to Abida et al., (1) both are expressed in an active form, (2) both have quite similar levels of expression, (3) both bind to Mex with affinity in the low pm range, and (4) both bind to Mtx using the same two-step mechanism (e.g., see columns 1 and 2 on page 893). However, this did not happen. Finally, Abida et al. admit that they don't know why these proteins exhibit different results (e.g., see Abida et al., page 893, column 2, "Further biochemical

characterization is needed to determine whether the variations in transcription levels result simply from differences in stability of the ternary complex or have more subtle implications for the mechanism by which transcriptional activators interact with the transcription machinery [i.e., the authors don't know the answer] ... it is interesting to speculate [i.e., guess] that transcription levels will not be solely due to a thermodynamic effect" (e.g., see page 893, column 2, paragraph 1 and 2).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicant's specification sets forth only one working example of the claimed method (e.g., see specification, Example 4). In this example, the non-covalent "GR-Dex" portion of the yeast three-hybrid-system shown in figure 13 was replaced with the "R61 PBP-cephem" group to provide a "covalent" interaction. That is, LexA-GR was replaced with LexA-R61 and Dex-Mtx was replaced with cephem-Mtx. The cepehm-Mtx was apparently synthesized by "analogy" to the Dex-cephem-Mtx shown in figure 21 (e.g., see specification, page 50, paragraph 1). In addition, one other "potential" species was suggested as being useful in this regard (e.g., see specification, page 49 where Fluorouracil-thymidylate synthase was disclosed; see also claim 34 wherein the thymidine synthase was claimed), but there is no evidence that a chemical inducer of dimerization ("CID") using this species (i.e., fluorouracil) was ever synthesized and tested.

(8) The quantity of experimentation needed to make or use the invention base on the

content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). Thus, due to the inadequacies of the instant disclosure (see above) one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 30-33 and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (Lin et al. "Dexamethasone-Methotrexate: An Efficient Chemical Inducer of Protein Dimerization In vivo" *J. Am. Chem. Soc.* **2000**, *122*, 4247-4248 and supplemental information pages S1-S12) (5/7/02 IDS for article) as evidenced by Simons (Simons et al. "Dexamethasone 21-mesulate: An affinity label of glucocorticoid receptors from rat hepatoma tissue culture cells" *PNAS* **1981**, *78*, 6, 3541-3545).

For ***claims 30 and 38***, Lin et al. (see entire document) disclose a yeast three-

A person shall be entitled to a patent unless -

hybrid assay using Dexamethasone-Methotrexate (e.g., see Lin et al, figure 1), which reads on the claimed invention. For example, Lin et al. disclose **(a)** forming a screening molecule by covalently bonding each molecule in the pool of candidate molecules to a substrate capable of selectively binding to and selectively forming a covalent bond with a receptor (e.g., see figure 1, wherein Mtx-linker-Dex is disclosed; see also page 4248 wherein FK506-linker-Dex is disclosed). Both the Mtx and FK506 are covalently bound to the Dex substrate via a linker. In addition, although Lin et al. fail to state that Dex is "capable" of forming a covalent bond with the receptor, the Examiner contends that this is an inherent property of the molecule as evidenced by Simons et al. (e.g., see Simons et al., page 3545, figure 6 showing covalent attachment of Dex to glucocorticoid receptor). Furthermore, Lin et al. disclose **(b)** introducing the screening molecule into a cell culture comprising cells that express a first fusion protein of a DNA-binding domain fused to a known target receptor domain against which the candidate molecule is screened (e.g., see figure 1 wherein a LexA-DHFR fusion protein is disclosed; see also Table 1 and figure 2 wherein a Yeast cell culture is used for screening via a β-galactosidase assay). Lin et al. also disclose a second fusion protein that comprises a receptor domain capable of binding to and forming a covalent bond with the screening molecule (e.g., see figure 1 wherein GR-B42 fusion is disclosed; see also Simon et al., page 3545, figure 6 showing that GR is "capable" of covalent attachment to the DEX). Lin et al. also disclose a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein (e.g., see figure 1 wherein the lacZ reporter gene is disclosed that is only activated when the LexA-DHFR and GR-B42 fusion proteins are

brought in close proximity by the heterodimeric ligand (e.g., Mtx-linker-Dex) via a standard yeast three-hybrid assay. Furthermore, Lin et al. disclose **(c)** permitting the screening molecule to bind to the first fusion protein and to the second fusion protein, bringing the two fusion proteins in to close proximity so as to activate the expression of the reporter gene (e.g., see figure 1, showing simultaneous binding of Mtx-linker-Dex to both LexA-DHFR and GR-B42 fusion proteins; see also Table 1 and figure 2 showing activation of β-galactosidase by activation of the lacZ gene). Finally, Lin et al. disclose **(d and e)** selecting the cell that expresses the reporter gene and identifying the small molecule that binds the known target receptor (e.g., see figure 2 showing selection and identification of Dex-Mtx under various conditions; see also page 4248, column 1, paragraph 1, "It is interesting to note, however, that in the yeast three-hybrid assay the absolute levels of β-galactosidase synthesis are 150-fold higher for Dex-Mtx than for Dex-FK506 at 1μ CID concentration based on liquid culture lacZ transcription assays [i.e., the Dex-Mtx was "identified" as the stronger binding candidate]").

For ***claim 31***, Lin et al. disclose yeast (e.g., see figure 1).

For ***claim 32***, Lin et al. disclose LexA (e.g., see figure 1).

For ***claim 33***, Lin et al. disclose B42 (e.g., see figure 1).

For ***claim 36***, Lin et al. disclose, for example, a combinatorial library consisting of two members (e.g., see page 4248, column 2, paragraph 1, disclosing a small library of "Dex" compounds including Mtx-linker-Dex and FK506-linker-Dex).

For ***claim 37***, Lin et al. disclose repeating the method steps for competitive binding (e.g., see page 4248, column 1, last paragraph, "A 10-fold excess of Mtx reduced

Dex-Mtx-dependent lacZ transcription to near background levels. A 10-fold excess of Dex, however, did not effect Dex-Mtx-dependent lacZ transcription, and higher concentrations of Dex were toxic to the yeast cells.").

For ***claims 38-40***, Lin et al. disclose, for example, Mtx-linker-Dex, which can bind to the "unknown" target to "function" as a biological bridge for promoting transcription of the lacZ gene when expressed in a Yeast three-hybrid assay. Furthermore, a DNA selected from the group consisting of genomic DNA, cDNA and synthetic DNA encodes the "unknown" target (e.g., see Supplementary Material, Construction of the LexA-DHFR and B42-rGR2 protein chimeras section starting on S6; see also 35 U.S.C. 112, second paragraph wherein the metes and bound of the term "unknown" cannot be determined).

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 30-33 and 36-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 133, 135-137, 141-147 and

150-160 of U.S. Patent No. 10/705,644 (referred to herein as '644) as evidenced by Fan et al. (Fan et al. "Covalent labeling of dihydrofolate reductase and folate transport proteins by fluorescein methotrexate" Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folid Acid Deriv., 9th (1990), Meeting Date 1989, 1162-5. Editor(s): Curtius et al. Publisher: de Gruyter, Berlin, Fed. Rep. Ger.). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986). Although the conflicting claims are not identical, they are not patentably distinct from each other because, for example, claims 30-33 and 36-40 are generic (or overlap in scope) to all that is recited in claims 133, 135-137, 141-147 and 150-160 of '644. That is, claims 133, 135-137, 141-147 and 150-160 of '644 fall entirely within the scope of claim 30-33 and 36-40 of the present application or, in other words, claims 30-33 and 36-40 of the present application are anticipated by claims 133, 135-137, 141-147 and 150-160 of '644.

For ***claims 30 and 38***, the '644 application also claims a method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules (e.g., see '644 application, preamble of claims 133 and 147). In addition, the '644 application also claims method steps for **(a)** forming a screening molecule by covalently bonding each molecule in the pool of candidate molecules to a substrate capable of selectively forming a covalent bond with a receptor (e.g., see claim 133(a), wherein the substrate is

methotrexate moiety of an analog of methotrexate; see also claim 147(a)). Furthermore, the '644 application also claims method steps for **(b)** introducing the screening molecule into a cell culture comprising cells that express a first fusion protein of a DNA-binding domain fused to a known target receptor domain against which the candidate molecule is screened (e.g., see the '644 application, claims 30(b) and 147(b); see also claims 141 and 152 wherein the DNA binding domain is disclosed as "DHFR-(DNA-binding domain)"). In addition, the '644 application discloses a second fusion protein which comprises a receptor domain capable of binding to and forming a covalent bond with the screening molecule (e.g., see claims 133(b) and 147(b)). The '644 application does not explicit state that the second fusion protein is "capable" of binding to and forming a covalent bond with the screening molecule but the Examiner contends that this limitation is inherently disclosed by the '645 application as evidenced by Fan et al. (e.g., see Fan et al., page 1162, paragraph 1 wherein methotrexate was shown as being "capable of covalently binding" to DHFR). The '644 application also discloses the use of a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein (e.g., see '644 application, claims 133(b) and 147(b)). The '644 application also discloses **(c)** permitting the screening molecule to bind to the first fusion protein and to the second fusion protein, bringing the two fusion proteins (e.g., see '644 application, claims 133(c) and 147(c)). Finally, the '644 application also discloses (d)-(e) selecting the cell that expresses the reporter gene and identifying the small molecules that binds the known target receptor (e.g., see '644 application, claims 133(d)-(e) and 147(d)-(e)).

For ***claim 31***, the '644 application also claims cells selected from the group consisting of insect cells, yeast cells mammalian cells and their lysates (e.g., see '644 application, claims 145 and 156 wherein mammalian and yeast cells are disclosed).

For ***claim 32***, the '644 application also claims a method wherein the DNA-binding domain of the first fusion protein is LexA (e.g., see '644 application, claims 142 and 152).

For ***claim 33***, the '644 application also claims a method wherein the transcription activation domain of the second fusion protein is B42 (e.g., see '644 application, claims 14 and 152).

For ***claim 36***, the '644 application also claims a method wherein the molecule is obtained from a combinatorial library (e.g., '644 application, claims 136 and 150).

For ***claim 37***, the '644 application also claims repeating the method steps for competitive binding (e.g., see '644 application, claims 137 and 151).

For ***claim 39***, the '644 application also claims a method wherein the unknown protein target is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA (e.g., see '644 application, claim 159).

For ***claim 40***, the '644 application also claims a method wherein the ligand has a known biological function (e.g., see claim 160).

This is a provisional obviousness-type double patenting rejection.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 24, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER

If attempts to reach the examiner by telephone are unsuccessful, the examiner's
applications is available through Private PAIR only. For more information about the PAIR